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RONALD I. EISENSTEIN
100 SUMMER STREET
NIXON PEABODY LLP
BOSTON, MA 02110

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,519	CANTOR ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,9,12 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,9,12 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-6, 9, 12, and 15-17 are pending and examined on the merits.

Please note: the text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/22/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 6/22/2007.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Withdrawn Claim Objections

1. The objections to claims 1 and 9 as set forth in the previous Office Action are **WITHDRAWN** in light of the amendments to the claims.

Withdrawn Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

2. The rejections of claims 1-8 and 19 under 35 U.S.C. 112, second paragraph, as being indefinite are **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

3. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is unclear over recitation of the phrase 'amplifying the diluted and undiluted nucleic acid sample, as recited in step (c) of claim 17. The phrase is unclear because claim 17 requires digesting a nucleic acid sample and diluting the digested sample (steps (a) and (b) of claim 17), thus the claim does not provide for any undiluted sample after step (b).

Withdrawn Claim Rejections - 35 USC § 102

4. The rejection of claims 1, 5, 6, and 19 under 35 U.S.C. 102(b) as being anticipated by Furlong et al et al (1993) is withdrawn in light of the amendments to claim 1 (i.e. the requirements of using mass spectrometric detection for genotyping and obtaining 12-18 genotype replicas) and the cancellation of claim 19.

Withdrawn Claim Rejections - 35 USC § 103

5. In light of the amendments to the claims, the rejections of claims under 35 U.S.C. 103(a) as being unpatentable over the teachings of the prior art are **WITHDRAWN**.

New grounds of rejection for the amended claims, as well as a Response to the pertinent arguments are set forth below.

New Claim Rejections - 35 USC § 103

6. Claims 1, and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (as cited in the IDS) in view of Furlong et al and Ross et al (1998).

Ruano et al teaches a method for the analysis of haplotypes amplified from a single DNA molecule.

Ruano et al teaches that a nucleic acid sample is diluted to form a solution containing a single copy of the target molecule (p.6297 – Dilutions; Fig 3), relevant to step (a) of claim 1. Relevant to step (b), the reference further teaches the amplification of target DNA using a primer pair (GR5 and GR6) that amplifies a region comprising polymorphic sites (Fig 1; p.6297 – Target for amplification) and subsequent analysis of the polymorphic positions (a TG deletion, two SNPs, and a TaqI RFLP site) in the amplified fragment (Fig 4). Relevant to step (c), Ruano et al teaches the genotyping of sites amplified from the single molecule dilution target DNA (Fig 4) by southern hybridization and restriction digestion, thus genotyping nucleic acid regions that contain polymorphisms. Relevant to step (d) of claim 1, Ruano et al teaches that additional experiments are performed on sample DNA to resolve constituent haplotypes of heterozygous individuals (p.6298, right col., last paragraph; Fig. 3; Fig 4), and that each experiment followed the scheme present in Figure 3 of the reference, thus comprising

steps (a)-(c) of claim 1. Relevant to step (e), the reference teaches that information regarding the individual genotypes is combined to determine the haplotype of the subject (Fig 4; p.6298 – Typing and direct haplotype determination of SMP products).

Regarding claims 4-6, Ruano et al teaches the analysis of a haplotype comprising polymorphic sites including single nucleotide polymorphisms and a dinucleotide insertion/deletion (Fig 1).

Ruano et al does not specifically teach an example in which a single molecule dilution is amplified in a multiplex PCR with at least four different primer pairs, relevant to the limitation of claim 1 step (b). Ruano et al does not specifically teach the analysis of 12-18 genotype replicas, relevant to the limitations of claim 1 step (d). Ruano et al does not teach using primer extension and mass spectrometric detection to perform genotyping, relevant to the limitations of claim 1 step (c).

Furlong et al teaches a method in which a single molecule dilution of a nucleic acid is amplified in a multiplex reaction for the determination of a haplotype (p.1192 – PCR of single sperm).

Regarding claim step (b) of claim 1, the reference specifically teaches the use of 4 different primer pairs to amplify four microsatellite regions on chromosome 9 (p.1192 – PCR primers; PCR of single sperm).

Neither Ruano et al nor Furlong et al teaches the analysis of amplified polymorphic genotype markers using primer extension and mass spectrometric detection.

Ross et al teaches methods of multiplex genotyping using primer extension and mass spectrometry (p.1347, right col., lns.3-11). The reference teaches a method comprising the steps of simultaneous amplification of 12 polymorphic loci and subsequent multiplexed primer extension using oligonucleotide primers and ddNTPS (p.1350 – Experimental protocol, PCR). The reference further teaches analysis of the primer extension products by MALDI-TOF mass spectrometry (p.1350 – Experimental protocol, MS; Fig.2).

Regarding the limitation of step (d) of claim 1, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45). It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al to produce and analyze 12-18 replicas. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the haplotype analysis methods of Ruano et al with the multiplex PCR methods of Furlong et al. One would have been motivated to do so because Furlong et al demonstrates the successful use of multiplex PCR for haplotype construction in the analysis of single molecules, and such a method would decrease the time and reagents required for the analysis of multiple polymorphic

regions comprising a haplotype. One would have been further motivated to perform a multiplex PCR reaction based on the assertion of Ruano that distant segments of an intact template molecule can be analyzed by PCR with multiple primer pairs for direct haplotype determination (p.6300 – Discussion), which is a process that would be used in a multiplex reaction as taught by Furlong.

It would further have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype analysis methods of Ruano et al in view of Furlong et al so as to incorporated the primer extension/mass spectrometry based genotype detection methods of Ross et al. One would have been motivated to use the methods of Ross et al based on the teachings of Ross et al that primer extension/mass spectrometry based methods eliminate excess handling and can resolve many possible genotypes/loci using a single non-fluorescent primer (p.1347, left col., ln.37).

Response to Remarks

Relevant to the presented rejection, Applicants have argued (p.11 of Remarks) that the combination of the cited references does not teach the combination of 'high multiplexing' (i.e. at least four different primer pairs) with the repetition of steps to obtain 12-18 genotype replicas. Applicants' arguments have been considered but are not found to be persuasive.

Applicants argue that the combination of the teachings of Ruano et al and Furlong et al would not be expected to result in an improvement over either technique. Applicants argue that Furlong et al teaches that 5% of results had to be discarded (i.e.

argued by applicant to be a rationale against performing replicas as taught by Ruano et al in the method of Furlong et al in view of teachings of Ruano et al which caution against contamination problems in dilute samples). Applicants further reason that Ruano et al explicitly cautions that one will have to optimize reaction conditions for each primer pair (i.e. argued by applicant to be a rationale against performing a multiplex of at least four primer pairs as taught by Furlong et al in the method of Ruano et al in).

With regard to the teachings of Furlong et al concerning discarding results and the caution of Ruano et al regarding contamination in dilute samples, Applicants arguments are not found to be persuasive because Furlong et al specifically states that it is unlikely that external contamination was the cause of the aberrant results that were discarded (p.1194, right col., lns.8-10). Additionally, while Ruano et al raises the issue of contamination in dilute samples, Ruano et al more specifically provides for methods to prevent contamination and controls to detect contamination, and particularly indicates that control experiments demonstrated that 'contamination was not a problem' (p.6297 – Prevention of contamination). Finally, with regard to discarded results, Furlong et al recognizes that the practical limitations of the single molecule dilution methodology (p.1194, right col., lns.7-8: 'flow-sorting of two sperm per well') may lead to data that is discarded, where Ruano et al specifically recognize the same practical limitations (p.6297, right col., lns.9-15: 'the remainder would contain multiple molecules'). Thus the argument that one would not multiplex in a method that includes single molecule dilution is not persuasive because both Furlong et al teaches aspects of both multiplexing and

dilution, and Ruano et al teaches aspects of single molecule dilution which Furlong et al asserts are important in the multiplex analysis of nucleic acids.

With regard to Applicants argument that one would not combine aspect of multiplex PCR analysis, as taught by Furlong et al, with the methods of Ruano et al because Ruano et al 'explicitly cautions that one will have to optimize reaction conditions for each separate primer pair' (Remarks p.11), Ruano et al specifically states that optimization of PCR procedures is required even for standard PCR protocols which do not comprise single molecule dilution, and that 'any primer pair with high specificity that functions robustly in standard PCR (product yield of 100 ng or more) should be usable for SMD analysis' (p.6297 – Booster PCR). Thus the optimization mentioned by Ruano et al is considered by Ruano et al to be routine experimentation that one of ordinary skill in the art would be required to perform for any PCR protocol. Furthermore, Furlong et al specifically recognizes aspects of PCR amplification that may be addressed with optimization (p.1194, right col., lns.1-4), where in regard to the amplification of abnormally sized products, the reference indicates that such amplification may be 'the product of PCR mispriming'. Thus Applicants argument that combining multiplexing and replications would hinder results because of the requirement of optimizing PCR conditions is not persuasive because Ruano et al teaches the routine nature of such optimization and the applicability of PCR procedures from standard PCR conditions to conditions comprising the single molecule dilution process.

The rejection as set forth is **MAINTAINED**.

7. Claims 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (as cited in the IDS) in view of Furlong et al and Ross et al (1998), and further in view of Drysdale et al (2000) (as cited in the IDS).

The teachings of Ruano et al in view of Furlong et al and Ross et al are applied to claims 3, and 9 as they were previously applied to claims 1 and 4-6.

Ruano et al in view of Furlong et al and Ross et al does not teach the comparison of a deduced haplotype with a haplotype from a control or a database of haplotypes to determine association of the haplotype with a biological trait, as required for claim 3, and step (e) of claim 9.

Drysdale et al teaches the use of β_2-adrenergic (β_2AR) receptor haplotypes in the prediction of response to albuterol (p.10486, left col., lns.6-8), which is a biological trait.

Regarding claim 3 and step (e) of claim 9 Drysdale et al teaches a collection of (β_2AR) haplotype pairs found in a cohort of asthmatics (p.10486, right col., lns.3-10; Table 2) (thus a database of haplotypes), as well as the association of the five most common haplotype pairs with patient response to albuterol (Fig.3; p.10487, left col., lns.1-25). The reference further teaches comparing a haplotype to the database of haplotypes and association data to determine association of the haplotype with a biological trait (Fig.3; p.10487, left col., lns.25-30).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have used the haplotype determination methods of Ruano et al in view of Furlong et al and Ross et al for the predictive analysis of haplotypes as taught

by Drysdale et al. One would have been motivated to do so based on the assertion of Drysdale et al that haplotypes are more predictive of phenotype, and that individual SNPs may have poor predictive power as pharmacogenetic loci (p.10488, right col., lns.13-17). With specific regard to claim 11, it would be obvious to create and analyze numerous replicas, including producing 12-18 replicas, to increase the accuracy of the analysis. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45).

Response to Remarks

Applicants' Remarks concerning the combination of the teachings of Ruano et al and Furlong et al (i.e. the combination of 12-18 replica genotypes and multiplexing using at least four primer pairs) have been addressed in the previous Response to Remarks. Furthermore it is noted that independent claim 9 requires only 'a multiplex amplification reaction with at least two primer pairs' (step (b) of claim 9. Thus Applicants arguments regarding the non-obviousness of requiring 'high multiplexing' of at least four primer pairs in combination with obtaining 12-18 replica genotypes is moot with regard to the limitations of claim 9.

The rejection as set forth is **MAINTAINED.**

8. Claims 12 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (as cited in the IDS) in view of Furlong et al and Ross et al (1998), and further in view of Rein et al (1998).

The teachings of Ruano et al in view of Furlong et al and Ross et al are applied to claims 12 and 15-17 as they were previously applied to claims 1 and 4-6.

Ruano et al in view of Furlong et al and Ross et al teaches a method for the analysis of haplotypes amplified in a multiplex PCR reaction from a single DNA molecule. Additionally, Ruano et al teaches the genotyping of sites amplified from the single molecule dilution target DNA by method including restriction digestion (Fig 3), and that information regarding the individual genotypes is combined to determine the haplotype of the subject (Fig 4; p.6298 – Typing and direct haplotype determination of SMP products). Thus, Ruano et al in view of Furlong et al and Ross et al provides steps (b)-(f) of claim 12, and steps (b)-(f) of claim 17. With particular regard to step (c) of claim 17, Ruano et al teaches the amplification of samples diluted to a single molecule concentration, as well as amplification of more concentrated samples (Fig 3; p.6297 – Standard PCR).

Ruano et al in view of Furlong et al and Ross et al does not teach an analysis of a nucleic acid sample that contains epigenetically modified nucleotides by specifically treating modified nucleotides (relevant to step (a) of claim 12) or digestion of a nucleic acid sample with a methylation sensitive restriction enzyme (relevant to step (a) of claim 17).

Rein et al teaches a method for the identification of 5-metyhlcytosine and related modifications in DNA genomes (Table 1; p.2255, right col., first full paragraph).

Regarding claim 12, Rein et al teaches methods for analysis of 5-methylcytosine (m^5C, which is a modified nucleotide) by treating genomic DNA with a composition that

differentially affects epigentically modified nucleotides by converting non-methylated C to U, and not altering m^5C (p.2258 – Differential base modification by bisulfite), relevant to step (a) of claim 12, thus effectively creating polymorphisms (the content at a given nucleotide position can be a C if the position is methylated, or U (which behaves similar to a T in subsequent base pairing processes) if the position is nonmethylated) based on the epigenetic methylation modification (Fig 2).

Regarding claim 15, Rein et al teaches the analysis of 5-methylcytosine (m^5C), which is a methylated nucleotide (p.2258 – Differential base modification by bisulfite).

Regarding claim 16, Rein et al teaches the use of bisulfite for the treatment of a nucleic acid sample (p.2258 – Differential base modification by bisulfite; Table 1; p.2255, right col., ln.25).

Regarding claim 17, Rein et al teaches methods for analysis of methylated bases at specific DNA sites use modification-sensitive restriction endonucleases (Table 1; p.2257 - Modification-sensitive restriction endonucleases (MSREs); Fig 1). Relevant to step (a) of claim 17, the reference teaches the digestion of a sample with restriction enzymes that are sensitive to base modification (i.e. will not digest methylated sites) and restriction enzymes that require base modification (i.e. will only digest methylated sites) (p.2257, left col., lns.14-24; Fig 1). Relevant to step (f) of claim 17, Rein et al teaches the analysis of the methylation dependent digestion of a sample by Southern analysis and PCR amplification (Fig 1; p.2258, left col., lns.15).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et

al in view of Furlong et al and Ross et al so as to have included the methylation analysis methods of Rein et al. One would have bee motivated to do so because Rein et al teaches that m^5C in the genomes of eukaryotic cells plays a role in a variety of processes (p.2255, left col., first paragraph of introduction). One would have been motivated to use the bisulfite treatment of Rein et al (relevant to claims 12, 15 and 16) because Rein et al teaches that such methods are highly sensitive, are amenable to rapid genomic sequencing, and provide positive display of m^5C (Table 1). One would have been motivated to use the MSRE method of Rein et al (relevant to claim 17) because Rein et al teaches that such methods provide a rapid analysis of large DNA regions, and are highly sensitive. With particular regard to step (f) of claim 17, the combination of the restriction enzyme digestion methods of Rein et al (as summarized in Fig 1 of Rein et al) and the haplotype determination methods of Ruano et al in view of Furlong et al and Ross et al would create a method where, for example, the DNA sample amplified by the multiplex PCR would be subjected to restriction digestion (as taught in Fig 1 of Rein et al) prior to amplification. Thus the determined haplotype would include polymorphic markers such as SNPs (determined by PCR as taught by Ruano et al) that are next to (e.g. the polymorphic sites would be adjacent to the cut site determined by the action of an m^5C-requiring restriction enzyme) the methylation site analyzed by the restriction enzyme.

Response to Remarks

Applicants' Remarks concerning the combination of the teachings of Ruano et al and Furlong et al (i.e. the combination of 12-18 replica genotypes and multiplexing

using at least four primer pairs) have been addressed in the previous Response to Remarks. Furthermore it is noted that independent claim 17 requires only amplifying a sample with 'least two different primer pairs in a multiplex amplification reaction' (step (c) of claim 17. Thus Applicants arguments regarding the non-obviousness of requiring 'high multiplexing' of at least four primer pairs in combination with obtaining 12-18 replica genotypes is moot with regard to the limitations of claim 17.

The rejection as set forth is **MAINTAINED.**

Maintained Rejection
Double Patenting

9. Claims 1, 3-6, 9, 12, and 15-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/542,043 in view of Furlong et al (1993).

Claims 1-18 of the conflicting application are drawn to the same methods as claims 1-18 of the instant application. Claims 1-18 of the conflicting application do not recite the limitation that a multiplex amplification reaction is performed. However such multiplex amplification reactions were well known in the art at the time the invention was made.

Furlong et al teaches a method in which a single molecule dilution of a nucleic acid is amplified in a multiplex reaction for the determination of a haplotype (p.1192 – PCR of single sperm). Regarding claim 19, the reference specifically teaches the use of 4 different primer pairs to amplify four microsatellite regions on chromosome 9 (p.1192 – PCR primers; PCR of single sperm).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of the claims of the conflicting application to include a multiplex PCR reaction as taught by Furlong et al, and further to specifically include at least 4 different primer pairs as taught by Furlong et

al. One would have been motivated to do so because Furlong et al demonstrates the successful use of multiplex PCR for haplotype construction in the analysis of single molecules, and such a method would decrease the time and reagents required for the analysis of multiple polymorphic regions comprising a haplotype.

This is a provisional obviousness-type double patenting rejection.

Response to Remarks

10. Applicants have noted (p.11 of Remarks) that a Terminal Disclaimer will be submitted with respect to application 10/542,043 should the claims in the instant application be found allowable. No such disclaimer is yet submitted, thus the rejection as set forth is **MAINTAINED.**

Conclusion

11. No claim is allowable. No claim is free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Stephen Kapushoc
Art Unit 1634

/Sarae Bausch/
Examiner, AU 1634